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Award Number: W81XWH-12-1-0487

TITLE: : A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis 1 (NF1)

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REPORT DATE: October 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2014	Annual	15 Sep 2013 - 14 Sep 2014

4. TITLE AND SUBTITLE: **A Phase II Trial on the Effect of Low-dose versus High-dose Vitamin D Supplementation on Bone Mass in Adults with** Neurofibromatosis 1 (NF1)

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-1-0487

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study has not been fully implemented. As a clinical trial the regulatory processes have taken more time than anticipated in the Statement of Work. This study has received an IND from the FDA to use high-dose vitamin D in the NF1 (neurofibromatosis type 1) population. The study was approved both by the University of Utah IRB and the DoD USAMRMC ORP HRPO in February, 2014. The University of Hamburg is working with the European Union Clinical Trials group (EurodratCT) to implement this study. A document of agreement has been executed between the University of Utah as the Legal Representative, or Sponsor, and the University Medical Center Hamburg-Eppendorf as the Delegated Institution. The Clinical Trials office in Hamburg is assessing the manufacture, shipment, and custodianship of study drug, cholecalciferol, from the manufacturer in Canada to the medical monitor at the U of Utah for relabeling, and final shipping to Germany. The U of Cincinnati has IRB approval, which will be reviewed by the U of Utah IRB prior to submission to the DoD HRPO for review. UBC has submitted final protocol revisions to its ethics committee. No funds have been allocated from Utah to the 3 participating centers.

15. SUBJECT TERMS
none listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	13	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION:

Neurofibromatosis type 1 (NF1) is a multisystem disease, and many patients have skeletal manifestations that fall into three general categories: (1) characteristic focal lesions, (2) short stature, and (3) osteomalacia, osteoporosis, or low BMD (bone mineral density), which occurs in almost all affected individuals by age 50. Vitamin D therapy appears to have some benefit in treating osteoporosis in the general population, and administration of vitamin D in a dose that maintains the serum 25-hydroxy vitamin D level above 30 ng/mL significantly improves BMD in individuals with NF1. These observations led to the development of a phase II clinical trial to evaluate the effectiveness of vitamin D_3 dosing in NF1 patients. This study is designed to assess the efficacy of oral vitamin D_3 and calcium therapy to prevent abnormal loss of bone mass in adults with NF1. The clinical trial is a double-blind, dose comparison of efficacy of high- versus low-dose vitamin D_3 on preservation of bone density as measured by DXA scanning after 2 years of treatment. It compares 2 groups of adults with NF1 between 25 and 40 years of age with insufficient levels of serum 25-hydroxy vitamin D at entry. Participants are randomized and one group will take 600 IU and the other will take 4,000 IU on a daily basis for 2 years. Participants and investigative teams are blinded to the vitamin D_3 dose. The primary outcome measure is bone mineral density at the spine and hip. Secondary patient reported outcome (PRO) measures include a quality of life questionnaire (SF-36), fracture history survey, and activity survey.

2. KEYWORDS:

25(OH)D = 25-hydroxy vitamin D
BMD = bone mineral density
CCTS = Center for Clinical & Translational Science at the University of Utah
Cholecalciferol=vitamin D3
CIN = University of Cincinnati enrollment center
CGRP = Clinical Genetics Research Program
DEXA = dual energy x-ray absorptiometry
Ddrops = formulation of cholecalciferol (vitamin D_3)
DXA = dual energy x-ray absorptiometry
FDA= Federal Drug Administration
HAM = University of Hamburg enrollment center
IRB = Institutional Review Board
NF1 = neurofibromatosis type 1
PCTO = Pediatric Clinical Trials Office at the University of Utah
PRO= Patient Reported Outcome
UBC = University of British Columbia enrollment center

3. OVERALL PROJECT SUMMARY (STATEMENT OF WORK)

Overall Objective: Determine best dose of cholecalciferol supplementation to optimize maintenance of bone mineral density in adults with neurofibromatosis type 1 (Funding: 9/30/2012 -09/29/2016; 48 months)

I. Major Goal - Assemble a cohesive multi-center team for phase II clinical trial

Task I.1 (mo 0-2): compile subcontracts between UTA and the following sites UBC (University of British Columbia, Canada), CIN (University of Cincinnati, USA), HAM (University of Hamburg, Germany).

Subcontracts have been distributed by the University of Utah Office of Sponsored Projects. The University of Cincinnati has signed the subcontract agreement, but has not submitted invoices. It has requested and we have granted carryover from year 1 to year 2, cognizant of the need hold funds for an extension of the study since it has been a year getting underway. The subcontract with the University of British Columbia will not be enacted until the investigators complete the Ethics Committee approval process. The University of Hamburg has begun the process with the European Union Clinical Trials group (EurodratCT), and the group identified a need for a designated legal representative from the sponsoring agency. The DoD decided that the University of Utah is the "sponsoring agency", and a document of agreement for responsibility of the clinical trial has been executed between the University of Utah as the Sponsor and the University Medical Center Hamburg-Eppendorf as a "Delegated Institution". An attempt to combine the subcontract with the sponsorship agreement was not successful, and a separate subcontract for distribution of funds to the University of Hamburg is under review. No funds have been allocated from Utah to the 3 participating centers.

Task I.2 (mo 2): conduct an organizational face-to-face meeting between 4 PIs and data monitor

This meeting is contingent on changes to protocol after IRB approval from all institutions, and it will be scheduled after approval from DoD USAMRMC ORP HRPO for all 4 sites.

Task I.3 (mo 2-3): assemble manual of operations and distribute to each site

A manual of operations has been drafted, and it is being amended as issues regarding protocols under review by IRBs at the respective institutions are modified. The manual will be finalized once the protocol has been approved by the DoD HSPO. A copy of the approved protocol at the University of Utah was included in the first annual review. This protocol served as the basis of the submission to the IRB of the University of Cincinnati and ethics committee of the University of British Columbia. An ethics committee to the University of Hamburg is pending resolution of clinical trials issues raised by the need

for compliance with regulations of the European Union Clinical Trials group.

Task I.4 (mo 1-2): establish lines of communication between PIs, coordinators, financial managers at each site

As part of the subcontracts appropriate financial managers have been identified at each of the 4 institutions. Email has been the primary line of communication. One conference call was conducted in April, 2014 to share the details of the U of Utah IRB documents that were approved by its IRB and the DoD HSPO. Ongoing communications are under development by the medical monitor group at the University of Utah.

Task I.5 (mo 2): establish long-term contract with courier for shipment of samples, supplies, study drug

A proposal with Markem, an international courier service, was initially established but is on hold until a review is completed by the University of Hamburg clinical trials office on the mechanism of shipment of drug after randomization by the medical monitor at the University of Utah. Negotiations on final pricing for shipping drug and serum samples has not been completed, pending changes that may be introduced by the IRB approval process at all 4 institutions.

Task I.6 (mo 7-48): maintain regular monthly reports regarding enrollment, data collection, and safety issues

Enrollment has not begun.

II. Major Goal - Enroll human subjects into a phase II clinical trial with vitamin D3 supplementation

Task II.1 (mo 0-5): establish IRB approvals at 4 sites and USAMRMC ORP HRPO review

Approval from the FDA to use the 4,000 IU dosing of cholecalciferol in the adult NF1 population was obtained in September of 2013. An annual report has been submitted to the FDA. The only significant change has been an alteration in the concentration of Ddrops. The manufacturer will provide a concentration of 300 IU/drop and a concentration of 2,000 IU per drop. Randomized participants will both take 2 drops per day instead of 1 drop per day.

IRB at the University of Utah approved the clinical trial application at the end of November, 2013.

USAMRMC ORP HRPO approved a modified U of Utah IRB-approved protocol in February, 2014.

UBC ethics committee review of a resubmitted application is underway.

U of Cincinnati IRB has been completed and will be submitted to the University of Utah IRB as part of the annual continuing review due in November, 2014.

U of Hamburg protocol is awaiting revisions as part of the clinical trials office review and compliance with the European Union regulations prior to submission to the ethics committee.

Task II.2 (mo 1): confirm oversight by an external safety monitor

The safety monitor is Dr. Richard Kanner from the Center for Clinical and Translational Sciences (CCTS) at the University of Utah, and he will serve as chair of a 3-member committee to oversee safety issues related to the study. They will meet face to face or by teleconference every 6 months to review recruitment and participant enrollment, monitor summarized data collection from the 4 sites as submitted to the Pediatric Clinical Trials Office (director, Dr. Michael Spigarelli), review adverse events, and monitor serum collection and disposition of samples. The amendment clarified his authority and responsibilities.

Task II.3 (mo 4-23): recruit adults with NF1 to consider participation in clinical trial

C*oordinators at each site have alerted their respective adult NF1 population of the upcoming trial. Recruitment will commence when all 4 sites have achieved institutional human subjects protection approval.*

Task II.4 (mo 3): establish failsafe mechanism to determine pregnancy status prior to densitometry

The manual of operations specifies local coordinator oversight of urine pregnancy testing prior to the initial DXA scan and exit DXA scan. Coordinators will review of reproductive history with females throughout the study.

Task II.5 (mo 6-15): first enrollment period for 25(OH)D serum screening/vitamin D3 supplementation

Pending IRB approval at all sites and final approval of the DoD HSPO.

Task II.6 (mo 18-23): second enrollment period for 25(OH)D serum screening/vitamin D3 supplementation

Not applicable.

Task II.7 (mo 6-15; mo 18-23): verify enrollment with unique identifier by hard copy and electronic means

Not applicable.

Task II.8 (mo 5-48): maintain ongoing IRB approval

Amendments will be introduced to each of the sites as a final DoD HSPO approval is established for all 4 sites. Approvals from the 3 subcontracted sites will be collated by the lead coordinator at the University of Utah. These will be forwarded to the DoD HSPO in a timely fashion.

Task II.9 (mo 12, 24, 36, 48): annual review by safety monitor and distributed to each IRB and USAMRMC

Per IRB stipulation, safety reviews of adverse events will take place every 6 months. Data including a spread sheet of all adverse events will be compiled by the coordinator at the University of Utah and submitted to the safety monitoring committee for review. The FDA also will be appraised of adverse events, and a summary of the safety monitoring committee will be provided to the FDA as part of the annual report of cholecalciferol use in adults with NF1.

Task II.10 (mo 18-27; mo 30-35): data monitor safety assessment for loss of bone mineral density of >7% loss

Not applicable.

III. Major Goal - Obtain laboratory, bone density, and survey data on participants in the study

Task III.1 (mo 3-5): establish scheduling processes for each enrollment center

Subcontracts are being finalized so work can begin at CIN, UBC, and HAM. Scheduling processes have been included in our application for CCTS services. The application for CCTS support at the University of Utah was reviewed by committee and approved in December, 2013.

Task III.2 (mo 3-5): complete assessment of cross-calibration of DXA machines at 4 sites

Pending subcontract completion.

Task III.3 (mo 2-5): assemble all data collection forms, blood collection kits, and CDs at each enrollment center

Clinical report forms have been included in IRB applications. A few have required revision as part of the approval process. Blood collection kits have been identified but not yet purchased.

Task III.4 (mo 3-5): establish and verify access to the study-specific, web-based, password-protected database

This will be accomplished in the Medical Monitor's office. Data submission will be set up at each of the 4 sites and data will be reviewed by the medical monitor team.

Task III.5 (mo 4): develop mechanism to obtain blood samples for 25(OH) vitamin D screening (ARUP Lab)

Pending final approval of contract with the shipping agency.

Task III.6 (mo 6-15; mo 18-23): obtain serum 25(OH)D on 316 enrollees across 4 enrollment centers

N/A

Task III.7 (mo 5-7): document processes for timely notification of serum 25(OH)D results and randomization

N/A

Task III.8 (mo 6-15; mo 18-23): Randomize 226 participants to either 600 IU or 4,000 IU of daily vitamin D3

N/A

Task III.9 (mo 6-15; mo 18-27; mo 30-39; mo 42-47): perform initial DXA scans, brief physical exam, and perform surveys on 226 participants at 3 time-points

N/A

IV. Major Goal - Monitor data acquired throughout the study period

Task IV.1 (mo 3-5): establish confidential procedures for monthly data acquisition monitoring and reporting

The medical monitor in the pediatric clinical trials office at the University of Utah have active procedures with other trials. Once IRB approvals are established and subcontracts have been fully executed at all sites, designated coordinators at each site will be trained in data submission with implementation of established procedures will begin.

Task IV.2 (mo 3-5): establish access for the data monitoring team to the study-specific database

CRFs have been provided to the data monitoring team under Dr. Spigarelli's direction. There is some hesitation in mobilizing the personnel until all sites have been reviewed by their home institution in case of revisions to University of Utah protocols.

Task IV.3 (mo 6-48): verify quality of data acquisition with coordinators at each

enrollment center

N/A

Task IV.4 (mo 18-21): perform interim analysis on a subset of enrollees at 1 year for change in BMD of hip

N/A

V. Major Goal - Provision of vitamin D3 and calcium supplementation

Task V.1 (mo 3-5): verify formulation of vitamin D3 in the form of Ddrops

Documentation has been provided by the manufacturer, Ddrops, on the formulation and distribution of batches of Ddrops to the University of Utah medical monitor team. The manufacturer has altered the concentrations of vitamin D3. Originally, it was to concoct concentrations of 600 IU per drop and 4,000 IU per drop. This has been modified to 300 IU per drop and 2,000 IU per drop. Thus, randomized participants will take 2 drops of either low-dose or high-dose vitamin D3.

Task V.2 (mo 5): distribute Ddrops from dispensing site in Ontario Canada to the University of Utah

This has not been initiated pending final IRB approvals and full execution of subcontracts between Utah and the other 3 participating centers.

Task V.3 (mo 2-4): establish failsafe methodology to mask the bottle of Ddrops and provide unique identifier

The medical monitor office has established the plan to remove the Ddrops manufacturer label and replace with a label that enables the randomization team to distribute the appropriate vial to the randomized participant at all 4 sites. This entails having the designated vials (low-dose and high-dose) in storage at the respective site's research pharmacy only to be released to a randomized participant by the site clinical research coordinator. Affirmation that the unique identifier of the participant is linked to a unique identifier on the vial will be performed by the local site coordinator and the data monitoring team, under the direction of the medical monitor.

Task V.4 (mo 6-15; 18-23): randomize participants with a unique bottle number/communicate to site coordinator

N/A

Task V.5 (mo 6-47): implement methods to educate/monitor participants on aspects of vit D3 and calcium intake

N/A

Task V.6 (mo 12-41): ensure resupply of Ddrops bottle corresponds to the initial bottle designation

N/A

Task V.7 (mo 6-48): monitor potential side effects of vit D3 supplementation

CRFs for adverse event reporting have been developed and included in the protocols submitted for IRB approval.

VI. Major Goal - Establish a bio-repository of serum samples

Task VI.1 (mo 2-5): develop protocol to process samples at the CGRP freezer storage facility at the U of Utah

This protocol has been approved by the FDA and the U of Utah IRB. Retention of serum after completion of the study has been addressed in IRB protocols. These specimens will be destroyed, unless the participant has signed other IRB approved consent for retention of sample for other studies.

Task VI.2 (mo 6-47): ensure participant identifier corresponds to consent to store samples for future studies

N/A

Task VI.3 (mo 6-47): document acceptance of storage sample in the CGRP database and vit D3 study database

The process for storage of sample in the CGRP database has been established, but linkage of information for the vitD3 study database has not been established.

VII. Major Goal - Data analyses

Task VII.1 (mo 6-48): collect data on all enrollees both by hard copy forms and in the study-specific database

N/A – no enrollees as of yet.

Task VII.2 (mo 6-48): validate data collection on a monthly basis by data monitor

N/A

Task VII.3 (mo 7-48): verify accuracy of data collection by enrollment center coordinators

N/A

Task VII.4 (mo 47-48): perform comparison of low-dose vit D3 versus high-dose vit D3 on data collections

N/A

Subcontracts between U of Utah (UTA) and CIN, UBC, and HAM

Organization name: Cincinnati Children's Hospital Medical Center (CIN)
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Organization name: University Medical Center Hamburg-Eppendorf (HAM)
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Investigators: Victor F. Mautner, MD Collaborators: Said Farschtshi, MD

4. KEY RESEARCH ACCOMPLISHMENTS – None to report

5. CONCLUSION: The implementation of this trial has been delayed for 2 primary reasons. The initial assessment by the University of Utah IRB that supplementation of vitamin D required an FDA exemption led to an application that resulted in a denial of exemption, and requirement for an IND for the administration of high-dose (4,000 IU) of cholecalciferol to a selected population of NF1 patients. Approval of an IND through the FDA was obtained in September of 2013. We could then begin the IRB approval process at the University of Utah, which was completed in November of 2013 and reviewed and approved by the DoD HSPO in February of 2014. The next major hurdle has been regulatory compliance with the European Union Clinical Trials organization

(EurodratCT) for implementation of a clinical trial through the University of Hamburg. We are working with EurodratCT to finalize our protocol, especially as it relates to the manufacture and transportation of study drug, cholecalciferol. We had anticipated working with University of Hamburg, but the additional regulatory oversight by the EurodratCT was not foreseen in our original application. The administrative costs of this additional regulatory component is provided by the University of Hamburg. Presently, we are working with the University of Hamburg to see if our protocol needs revisions prior to giving the green light for recruitment and enrollment in the study.

It is important to obtain appropriate approval from the University of Hamburg because it has the highest anticipated number of enrollees for this study. Germany does not fortify foods with vitamin D, and Dr. Mautner's clinic includes many adults who would be willing to participate and likely have insufficient levels of serum 25-OH vitamin D. Recruitment from other sites, including North American NF lay organizations, is a potential option if the details of drug procurement and transportation cannot be worked out with the EurodratCT office and the University of Hamburg. This would entail travel costs for participants to be seen at one of the 3 North American sites, which would require review and approval by the U.S. Army Medical Research and Materiel Command office.